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# HEPATITIS C VIRUS (HCV) INFECTION AND LYMPHOPROLIFERATIVE DISORDERS

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## 1. ABSTRACT

Several infectious agents have been associated with development of lymphoproliferative disorders. Among these is hepatitis C virus (HCV), which infects more than 200 million people worldwide. HCV infection has been linked to progression of type II mixed cryoglobulinemia (MC) syndrome and has also been suggested to contribute to development of B-cell non-Hodgkin's lymphoma (NHL). Mechanisms responsible for development of lymphoproliferative disorders among HCV-positive patients remain unclear. Accumulating evidence supports a model in which chronic stimulation of B-cells by antigens associated with HCV infection causes nonmalignant B-cell expansion that may evolve into B-cell NHL. The course of disease among HCV-positive B-cell NHL patients may be complicated by coinfection with other infectious agents. This possibility has been explored by studies that have investigated potential interactions between HCV and human immunodeficiency virus (HIV) as well as between HCV and Epstein-Barr virus (EBV). Further characterization of the mechanisms by which HCV promotes development of lymphoproliferative disorders may improve diagnosis, classification, and treatment of these conditions.

## 2. INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem. More than 200 million people are currently infected with HCV worldwide. It is well established that HCV infection is associated with chronic hepatitis, cirrhosis, and hepatocellular carcinoma. HCV infection is also associated with several extrahepatic conditions, including autoimmune disease, type II mixed cryoglobulinemia (MC) syndrome, and B-cell non-Hodgkin's lymphoma (NHL) (1-5). HCV is a positive stranded RNA hepacivirus from the Flaviviridae family. The HCV genome consists of approximately 9600 nucleotides and has a single open reading frame (6). This open reading frame encodes a polyprotein that is cleaved into functional viral proteins by proteases encoded by the virus as well as the host. The amino terminal proteins, including core, envelope glycoprotein-1 (E1), and E2, have structural functions. The remaining proteins, such as protease, RNA helicase and RNA dependent RNA polymerase, have nonstructural functions (7).

Nucleotide sequence analysis of different HCV isolates revealed several distinct genotypes (8). The distribution of HCV genotypes varies throughout the world.

The most common HCV genotypes in North America are 1a and 1b. The most common HCV genotypes in Italy, Egypt, and South Africa are 1b, 4a, and 5a, respectively (9, 10). HCV genotype 6a is primarily restricted to Hong Kong, Macau, and Vietnam (11-14). Testing for the presence of anti-HCV antibodies in serum is the primary method used to diagnose HCV infection. An enzyme immunoassay (EIA) is used first as a screening test. Positive EIA results are then confirmed by a recombinant immunoblot assay (RIBA). Both of these assays detect antibodies against HCV proteins (15). Anti-HCV antibodies can be detected in approximately 60% of patients at the onset of symptoms and in approximately 90% of patients after three months of HCV infection. Sera that test positive for anti-HCV antibodies are subsequently tested for the presence of HCV RNA by a reverse transcription-polymerase chain reaction (RT-PCR) assay (16). HCV RNA can generally be detected within three weeks after infection. HCV infection is cleared by an estimated 20% of infected individuals. The remainder of infected individuals become chronically infected.

## 3. TYPE II MIXED CRYOGLOBULINEMIA SYNDROME

HCV infection is closely associated with development of type II MC syndrome. Approximately 90% of patients with type II MC are HCV-positive (2). Clinical manifestations of type II MC syndrome include cutaneous vasculitis, nephritis, peripheral neuropathy, and B-cell proliferation (2). Type II MC syndrome has also been proposed to be a precursor of B-cell NHL. A characteristic histologic feature of chronic HCV infection is the presence of lymphoid follicles in the liver (17, 18). Mononuclear cells in liver biopsies from patients with type II MC syndrome consist primarily of B-cells that express immunoglobulin M (IgM) (19, 20). Monoclonal IgM with rheumatoid factor (RF) activity is present in the serum of patients with type II MC syndrome. Monoclonal IgM RFs (mRFs) present in type II MC syndrome patients originate primarily from the liver and bone marrow (18, 21, 22).

Type II MC syndrome has been suggested to develop as a consequence of chronic antigenic stimulation. Involvement of chronic antigenic stimulation in development of type II MC syndrome is supported by idiotypic similarities that exist between mRFs from different patients with the disease. Sera from approximately 80% of these patients contain mRF with the WA cross-reactive idiotype (CRI), which was named after the patient in whom it was originally identified (23). Other CRIs common among mRFs from type II MC syndrome patients include Po and liver cytosol-1 (LC1). The idiotypic similarities shared by mRFs from different patients with type II MC syndrome correspond with the restricted set of rearranged immunoglobulin (Ig) genes that encode mRFs. *IGHV1-69*, *IGHV3-23*, and *IGKV3-20* are associated with the WA CRI, *IGHV3-7* and *IGKV3-15* are associated with the Po CRI, and *IGHV4-59* is associated with the LC1 CRI. The restricted use of a specific set of Ig genes for mRF synthesis suggests that a specific antigen contributes to development of type II MC syndrome.

B-cell proliferation in patients with type II MC syndrome may be a consequence of genetic changes that enhance B-cell survival. Bcl-2 is an antiapoptotic protein that is expressed at elevated levels within bone marrow and hepatic lymphoid infiltrates of most patients with type II MC syndrome (20). Sequence analysis of rearranged Ig heavy chain genes within hepatic lymphoid infiltrates of patients with type II MC syndrome indicates that these infiltrates are composed of monoclonal or oligoclonal B-cell populations (24-26). This analysis also suggests that rearranged Ig genes from these B-cell populations undergo somatic hypermutation (SHM) that generates intraclonal diversity (27, 28).

## 4. DEVELOPMENT OF B-CELL NHL IN THE PRESENCE OF HCV INFECTION

Many studies have provided evidence that HCV infection is associated with development of both indolent and aggressive B-cell NHL (29-34). Lymphoplasmacytoid lymphoma (immunocytoma) has been observed to have a particularly close association with HCV infection (35, 36). A recent case control study of patients with various B-cell NHL subtypes indicated that HCV infection was detected most frequently among those with diffuse large B-cell lymphoma (DLBCL) (Figure 1) (34).

Analyses of HCV genotypes among infected B-cell NHL patients have yielded conflicting results. Two studies indicated that HCV genotype 2a was more common among patients with monoclonal gammopathy than control subjects (9, 10). HCV genotypes 2a or 2c were observed to be more common among B-cell NHL patients than either blood donors or individuals with chronic liver disease (37). The ratio of HCV genotypes 2a or 2c to HCV genotype 1b was higher among B-cell NHL patients than control subjects, but this difference was not statistically significant (34). In contrast, another study did not observe any difference in the distribution of HCV genotypes between Italian B-cell NHL patients and control subjects (30). The HCV genotype distribution observed among both groups was similar to previous estimates of the HCV genotype distribution among the Italian population (38-40).

Direct infection of B-cells by HCV has been proposed as a possible step in B-cell NHL development. B-cells have been shown to be susceptible to HCV infection both *in vitro* and *in vivo* (41, 42). RT-PCR, *in situ* hybridization, and immunochemistry studies have demonstrated that HCV colocalizes with low grade B-cell NHL tissue (43-45). However, HCV-positive cells were primarily located along the edges of low grade B-cell NHL tissue and were only rarely observed to be interspersed within it (43-45). Additionally, neoplastic tissue biopsies from two HCV-positive patients with high grade B-cell NHL were found to be HCV-negative (46). These findings suggest that direct infection of B-cells is unrelated to progression of B-cell NHL among HCV-positive patients.

Convincing evidence suggests that chronic antigenic stimulation promotes B-cell NHL development among HCV-positive patients. Sequence analysis of

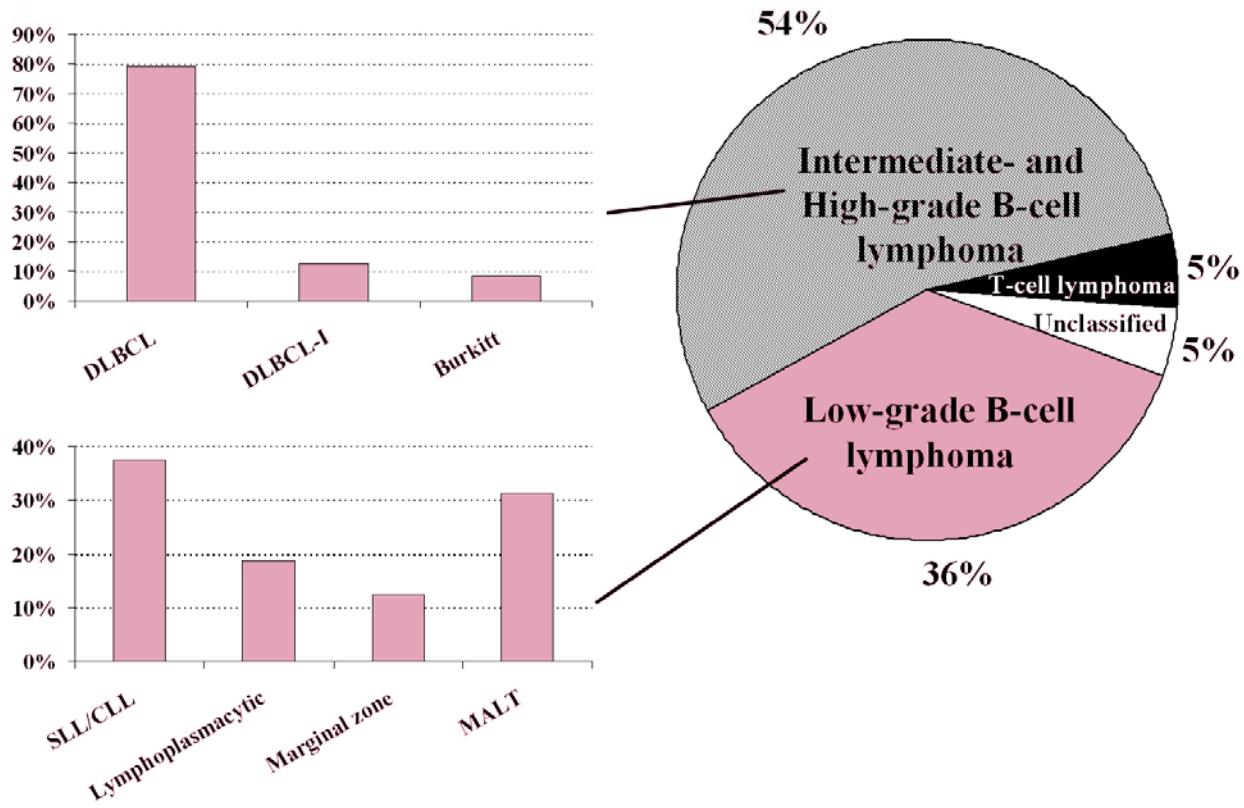


**Figure 1.** Distribution of B-cell NHL subtypes among HCV-positive patients (34).

rearranged Ig genes in malignant B-cells from HCV-positive patients reveals that certain combinations of heavy and light chain genes are frequently present. Common combinations include *IGHV3-23*/*IGHD3-22*/*IGHJ4*, *IGHV1-69*/*IGHD3-22*/*IGHJ4*, or *IGHV4-59*/*IGHD2-15*/*IGHJ2* with either *IGKV3-20*/*IGKJ1* or *IGKV3-20*/*IGKJ2* and *IGHV3-7*/*IGHD3-16*/*IGHJ3* or *IGHV3-7*/*IGHD3-22*/*IGHJ3* with *IGKV3-15*/*IGKJ1* (Figure 2) (27, 45, 47-50).

Many of the most common rearranged Ig genes present in malignant B-cells from HCV-positive patients with B-cell NHL are identical to those that frequently encode mRFs in individuals with type II MC syndrome (47, 48). It has also been observed that complementarity determining regions (CDRs) of rearranged Ig genes encoding RFs as well as those present in malignant B-cells from HCV-positive patients with B-cell NHL have a low ratio of replacement to silent mutations (46, 47, 51). This scarcity of replacement mutations suggests that there is selective pressure against evolution of antibodies with higher antigen binding affinity in type II MC syndrome as well as B-cell NHL among HCV-positive patients. The similarities shared by rearranged Ig genes present in B-cells from patients with type II MC syndrome and malignant B-cells from HCV-positive patients with B-cell NHL support the possibility that the antigens involved in promoting type II MC syndrome development are the same as those involved in promoting B-cell NHL development among HCV-positive patients. These similarities also support the possibility that type II MC syndrome is a precursor of B-cell NHL.

Antigens associated with HCV infection are suspected to contribute to development of type II MC syndrome and B-cell NHL among HCV-positive individuals. This is supported by analysis of Ig genes used to express anti-HCV antibodies. IGHV1-69 was the $V_H$ gene most frequently used to encode anti-HCV antibodies that recognize E2 (52). Similarly, IGHV1-69 is commonly used to express mRFs with the WA CRI in individuals with type II MC syndrome and is commonly present in malignant B-cells from HCV-positive B-cell NHL patients. Furthermore, an antibody encoded by mRNA isolated from an HCV-positive patient with DLBCL was observed to bind to E2 (5). These results provide evidence that E2 may be an important antigen involved in promoting development of type II MC syndrome and B-cell NHL among HCV-positive individuals.

Cluster of differentiation-81 (CD81) has been proposed to be involved in chronic antigenic stimulation associated with HCV infection. CD81 is a cellular ligand for E2 that is expressed by most human cell types, but not red blood cells or platelets (53-55). CD81 is a member of the tetraspanin protein family and contains four transmembrane domains and two extracellular loops. Binding of E2 is mediated by the large extracellular loop

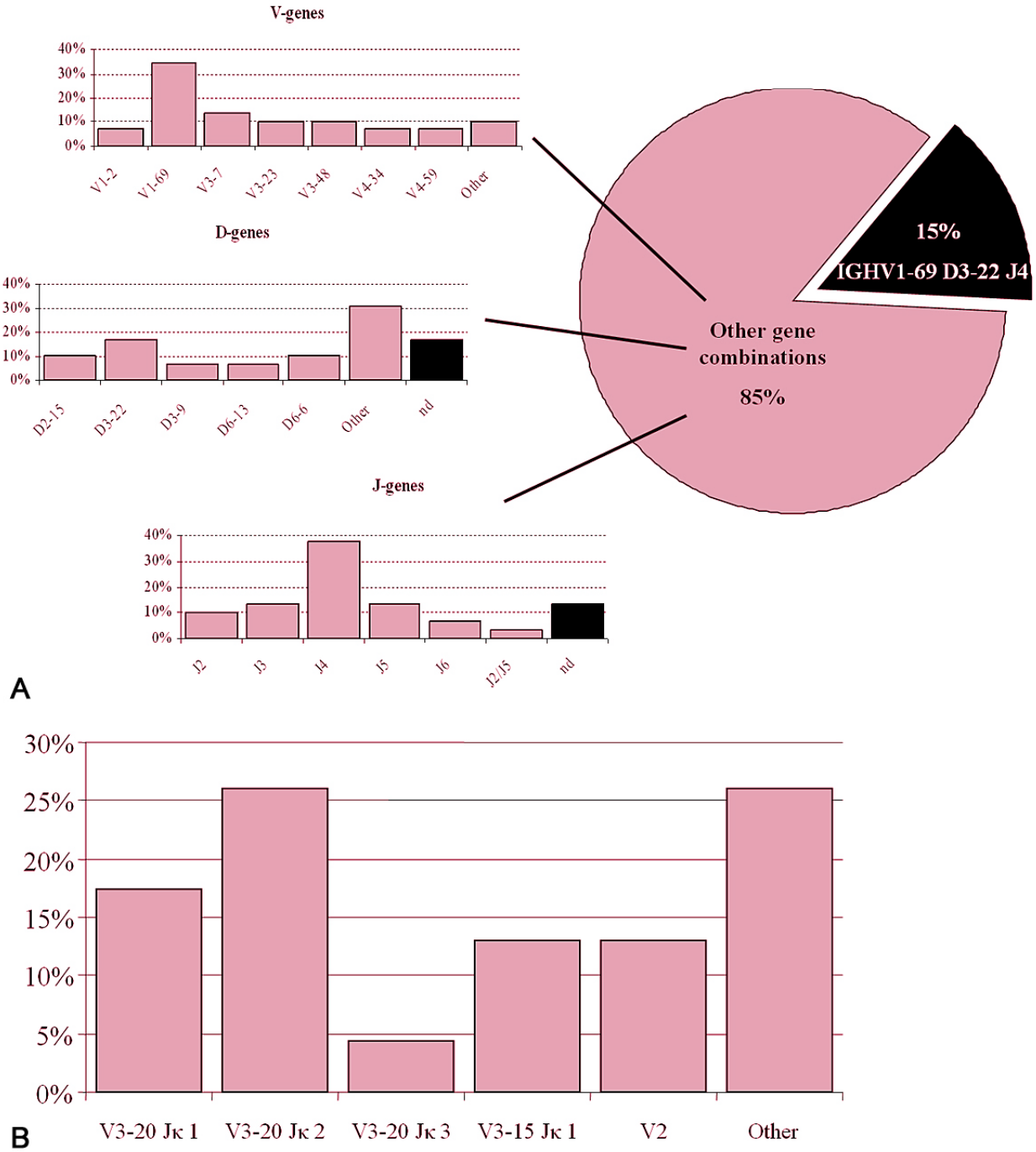


**Figure 2.** Distribution of $V_H$, $D_H$, and $J_H$ genes (A) and $V_\kappa$ and $J_\kappa$ genes (B) rearranged in B-cell NHL tissue from HCV-positive patients.

(LEL) of CD81 (54-56). Two separate CD81 binding sites have been identified on E2 (57-59). Binding of HCV to CD81 alone is insufficient for viral infection. This is illustrated by the observation that tamarins from the *Saguinus* genus of New World monkeys are not susceptible to HCV infection even though tamarin CD81 binds E2 with higher affinity than human CD81 (60, 61).

CD81 is a component of a multimeric protein complex on the cell surface of mature B-cells. Other proteins from this complex include CD19, CD21, and Leu-13 (62). Simultaneous binding of antigens to this complex and the B-cell receptor (BCR) has been suggested to facilitate B-cell proliferation (63). Binding of HCV to CD81 as well as the BCR may induce nonmalignant

polyclonal B-cell expansion. Genetic changes may later lead to malignant transformation of these B-cells and development of B-cell NHL.

### 4.1 Rearrangement of *bcl-2* in lymphoproliferative disorders associated with HCV infection

The t(14;18)(q32;q21) translocation is a genetic abnormality associated with B-cell NHL. This translocation fuses the *bcl-2* proto-oncogene with *IGH* and consequently causes Bcl-2 overexpression. Rearrangement of *bcl-2* has been associated in particular with B-cell NHLs for which an antigen driven mechanism has been proposed, such as follicular lymphoma (FL) (64, 65). Previous studies have shown that *bcl-2* rearrangement was common in peripheral blood mononuclear cells (PBMCs) of HCV-positive patients with type II MC (66-68). This translocation has therefore been postulated to contribute to B-cell NHL development by preventing B-cell apoptosis (69).

Rearrangement of *bcl-2* was infrequently detected within neoplastic tissue from HCV-positive B-cell NHL patients, except those with mucosa-associated lymphoid tissue (MALT) lymphoma (70). The frequency of *bcl-2* rearrangement among MALT lymphoma patients was observed to be higher among HCV-positive patients than those that are HCV-negative (71). Nucleotide sequence analysis of t(14;18)(q32;q21) translocations in MALT lymphomas associated with HCV infection revealed that *bcl-2* was joined to $J_H6$ in each patient (72). Joining of *Bcl-2* to $J_H6$ was similarly found to occur more frequently in leukocytes from HCV-positive individuals without B-cell NHL than from those that are HCV-negative (73). The apparent preference for joining of *bcl-2* to $J_H6$ among HCV-positive individuals with and without B-cell NHL remains to be explained.

### 4.2 Genetic mutations associated with B-cell NHL among HCV-positive patients

SHM is a process that enhances antibody affinity for a particular antigen by introducing nucleotide substitutions within the immunoglobulin variable (IgV) genes of germinal center (GC) B-cells (74). Specific features of SHM include the predominance of single base substitutions, preference for transitions over transversions, and specific targeting of AG/G/CT/AT (RGYW) motifs. The *bcl-6* proto-oncogene is another target of SHM in GC B-cells. Bcl-6 is a transcriptional repressor that regulates B-cell maturation (75). Genetic mutation arising from aberrant SHM has been proposed to contribute to B-cell NHL. DLBCLs frequently exhibit evidence of aberrant SHM of the coding sequence or 5'-untranslated region (5'-UTR) of proto-oncogenes that have been implicated in the pathogenesis of lymphoid malignancies, including *PIM-1*, *PAX-5*, *RhoH*/*TTF*, and c-*myc* (76). Frequent aberrant SHM of *PIM-1*, *PAX-5*, *RhoH*/*TTF*, and *c-myc* has also been observed in NHLs associated with acquired immunodeficiency syndrome (AIDS) as well as primary central nervous system lymphomas (PCNSLs) (77, 78).

The potential contribution of aberrant SHM to the development of B-cell NHL among HCV-positive patients was recently examined (79). Analysis of *PIM-1*, *PAX-5*, *RhoH*/*TTF*, and *c-myc* gene mutations within B-cell NHL tissue from HCV-positive patients did not reveal statistically significant clustering of mutations within RGYW motifs (79). However, clustering of *bcl-6* mutations with RGYW motifs demonstrated that the SHM process remained active in the presence of HCV infection. The pattern of *PIM-1*, *PAX-5*, *RhoH*/*TTF*, and *c-myc* gene mutations was similar to the pattern of *beta-catenin* and *p53* gene mutations in B-cell NHL tissue from HCV-positive patients analyzed in a separate study (80). It has been proposed that genetic mutations in tumors from HCV-positive patients arise from induction of error prone DNA polymerase activity by HCV infection instead of aberrant SHM (80).

## 5. OTHER INFECTIOUS AGENTS ASSOCIATED WITH B-CELL NHL DEVELOPMENT

Several infectious agents have been linked with B-cell NHL in addition to HCV (81, 82). *Borrelia burgdorferi*, *Campylobacter jejuni*, *Chlamydia psittaci*, and *Helicobacter pylori* have been suggested to contribute to development of MALT lymphomas of the skin, small intestine, ocular adnexa, and stomach, respectively (83-86). Human T-cell lymphotropic virus-1 is associated with acute T-cell leukemia/lymphoma, human immunodeficiency virus (HIV) is associated with several high grade B-cell NHLs, and infection of immunosuppressed individuals with Epstein-Barr virus (EBV) is associated with endemic Burkitt's lymphoma as well as immunoblastic lymphoma (87, 88). A recent study also provides evidence that hepatitis B virus (HBV) may contribute to development of B-cell NHL (34). It is possible that progression of B-cell NHL among HCV-positive patients may be affected by coinfection with other infectious agents associated with B-cell NHL development.

### 5.1 Interactions between HCV and HIV in B-cell NHL patients

Epidemiologic and experimental data suggest a role for HIV infection during development of various tumors (88-91). Improved survival of HIV-positive patients since the development of highly active antiretroviral therapy (HAART) may increase the likelihood that these individuals will become coinfected with other infectious agents. Among these infectious agents is HCV. Approximately 30% of HIV-positive patients from Europe and North America are coinfected with HCV. This frequency increases to 50-90% among those that contracted HIV by using contaminated needles to inject drugs (92). Several studies indicate the risk of cirrhosis and hepatocellular carcinoma among HCV-positive patients is increased by HIV coinfection (93, 94). HCV coinfection may also increase the hepatotoxicity of antiviral therapy (95). In contrast, clinical progression of HIV infection and the risk of B-cell NHL development among HIV-positive patients were both unaffected by HCV coinfection (96-98).

### 5.2 Interactions between HCV and EBV in B-cell NHL patients

It has previously been suggested that EBV and HCV infections cooperate in a synergistic manner to

promote B-cell proliferation (99). Both EBV and HCV deliver stimulatory signals to B-cells by binding to the same cell surface protein complex. This complex contains CD21, which binds EBV, and CD81, which binds E2 (54). Binding of E2 to CD81 has been proposed to provide a costimulatory signal to B-cells infected with EBV (54, 100). EBV infection induces expression of LMP1, which promotes B-cell immortalization (101, 102).

It was recently demonstrated that $V_H$ and $V_L$ genes expressed by neoplastic B-cells from patients coinfected with EBV and HCV are among those previously reported to be most common among HCV-positive B-cell NHL patients (50, 103). This observation suggests that HCV infection may have contributed to development of B-cell NHL in these patients. However, neoplastic B-cells from these patients expressed LMP1 and exhibited a lack of intraclonal variation, which is in agreement with previous analyses of other B-cell lymphoproliferative disorders associated with EBV infection (104-106). These findings indicate that EBV infection may have prevented evolution of variant neoplastic B-cell clones by suppressing antibody affinity maturation. It is possible that interactions between EBV and HCV accelerate the course of disease in coinfected B-cell NHL patients.

## 6. ANTIVIRAL TREATMENT OF HCV-POSITIVE PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS

Treatment of HCV infection has been proposed as a complementary therapeutic approach to treat B-cell NHL among HCV-positive patients. A similar strategy has been used successfully to treat MALT lymphomas associated with *Helicobacter pylori* infection (107). Several independent studies support the possibility that HCV-positive B-cell NHL patients may benefit from antiviral therapy. Interferon-alpha-2b (IFN-alpha-2b) treatment reversed monoclonal B-cell expansion among HCV-positive patients with type II MC syndrome (108). Loss of detectable t(14;18)(q32;q21) among PBMCs was frequently achieved in HCV-positive patients treated with either IFN-alpha alone or IFN-alpha plus ribavirin (109, 110). IFN-alpha-2b alone or IFN-alpha-2b plus ribavirin also induced regression of splenic lymphoma with villous lymphocytes in all HCV-positive patients receiving treatment. In contrast, HCV-negative controls did not benefit from antiviral therapy (111). Treatment with pegylated IFN-α plus ribavirin has more recently been shown to be useful for treatment of low grade B-cell NHL among HCV-positive patients (112). The effectiveness of antiviral treatment for type II MC syndrome or B-cell NHL among HCV-positive patients provides evidence that HCV infection contributes to the development of these conditions.

## 7. CONCLUSION

Epidemiological and experimental studies have provided evidence that HCV infection contributes to B-cell NHL development. It has also been suggested that B-cell expansion among HCV-infected patients can be prevented by antiviral treatment. Numerous studies support the possibility that HCV infection promotes B-cell NHL development by an antigen driven mechanism. However, no specific antigen has yet been identified. Potential interactions between HCV and other viruses in B-cell NHL patients have also been analyzed. Studies have thus far demonstrated that there is no major interaction between HCV and HIV during B-cell NHL progression in coinfected patients. Further characterization of the mechanisms by which HCV infection contributes to B-cell NHL development may improve its diagnosis, classification, and treatment.

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**Abbreviations:** AIDS: acquired immunodeficiency syndrome; BCR: B-cell receptor; CD19: cluster of differentiation-19; CD21: cluster of differentiation-21; CD81: cluster of differentiation-81; CDRs: complementarity determining regions; CLL: chronic lymphocytic leukemia; CRI: cross-reactive idiotype; DLBCL: diffuse large B-cell lymphoma; DLBCL-I: immunoblastic DLBCL; E1: envelope glycoprotein-1; E2: envelope glycoprotein-2; EBV: Epstein-Barr virus; EIA: enzyme immunoassay; FL: follicular lymphoma; GC: germinal center; HAART: highly active antiretroviral therapy; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN-alpha: interferon-alpha; Ig: immunoglobulin; IgM: immunoglobulin M; IgV: immunoglobulin variable; LC1: liver cytosol-1; LEL: large extracellular loop; MALT: mucosa-associated lymphoid tissue; MC: mixed cryoglobulinemia; mRFs: monoclonal IgM RFs; NHL: non-Hodgkin's lymphoma; PBMCs: peripheral blood mononuclear cells; PCNSLs: primary central nervous system lymphomas; RF: rheumatoid factor; RIBA:

recombinant immunoblot assay; RT-PCR: reverse transcription-polymerase chain reaction; SHM: somatic hypermutation; SLL: small lymphocytic lymphoma.

**Key words:** Acquired immunodeficiency syndrome, B-Cells, Cancer, Epstein-Barr virus, Hepatitis C virus, Human immunodeficiency virus, Immune response, Immunity, Lymphoid tissue, Mononuclear cells, Tumor, Lymphoma, Non-Hodgkin's lymphoma, Review, Rheumatoid factor

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